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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,093	09/29/1999	KAZUHIRO OHSUYE	47259-0373	5533

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EXAMINER	
SLOBODYANSKY, ELIZABETH	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,093	OHSUYE ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-97* is/are pending in the application.

4a) Of the above claim(s) *78,80,81 and 84-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-77,79 and 94-97* is/are rejected.

7)☒ Claim(s) *82 and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 July 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The statement in the Office action mailed February 2, 2006 (page 2) should read: The amendment filed November 8, 2005 amending claims 82-93, 96 and 97 has been entered.

The amendment filed May 19, 2006 amending the specification to insert references to the sequence identifiers has been entered.

The substitute Sequence Listing and the computer readable form thereof filed May 19, 2006 have been entered.

Claims 54-97 are pending.

Election/Restrictions

Applicant's election with traverse of species of SEQ ID NO:20 in the reply filed on May 19, 2006 is acknowledged. The traversal is on the ground(s) that "Applicants note for the record that the PCT rules do not support the legal concept of "species" as practiced under Title 37 of the Code of Federal Regulations and associated rules and statutes for restriction practice for applications which are not filed under 35 U.S.C. § 371. The election reads upon claims 54-83 and claims 90-97" (Remarks, page 5). This is not found persuasive because, indeed this application is filed under 35 U.S.C. § 371. Furthermore, in fact PCT Rules 13.1 and 13.2 govern the election of species in national stage applications.

The requirement is still deemed proper and is therefore made FINAL.

Claims 78, 80, 81 and 84-93 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 19, 2006.

NOTE: "The structure of the fusion protein, GP97ompPR (SEQ ID NO: 20), is depicted in Figure 7. In this figure, amino acids 1-110 comprise the protective peptide. Amino acids 111-123 comprise the helper peptide" (Applicants' Remarks of May 19, 2006, page 5). Residues 124-154 correspond to SEQ ID NO:28 that comprises SEQ ID NO:27 and comprises neither SEQ ID NO: 5 nor SEQ ID NO:8 (claims 90-91).

Drawings

The drawings filed July 26, 2001 are objected to under 37 CFR 1.83(a). Figure 24B shows "GLP-1 (7-36)NH" whereas "GLP-1 (7-36)NH_2" should be shown.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the

brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following: the description of Figure 24 recites "C" and "D" whereas Figure 24 shows "A" and "B". Further, it recites "GLP-1(G) whereas the figure shows "GLP-1 (7-36)NH_2". In addition, "NaCl" is mistyped (substitute specification filed July 5, 2005).

Appropriate correction is required.

Claim Objections

Claim 97 is objected to as dependent from non-elected claims 84-89.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

> same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54-77, 79 and 94-96 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 54-77, 79 and 94-96 are drawn to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a peptide of interest, a vector and a cell comprising said DNA.

Claims 54-62, 67, 68, 72, 73, 76 do not limit a peptide of interest by either structure or function. Claims 63-66, 69-71, 74, 75 and 77 limit peptide of interest to glucagons-like peptide-1 derivative. Claims 94-96 limit peptide of interest to the specific sequence. However, said claims comprise helper peptide of any structure and function. Therefore, claims 54-77, 79 and 94-96 recite either a genus of peptides of interest and/or a genus of helper peptides and a genus of protective peptides. These genera encompass an infinite number of peptides of any structure and from any source both naturally occurring and man made as long as the isoelectric point of the peptide of interest connected to a helper peptide is between 8-12.

As mentioned above, claims 63-66, 69-71, 74, 75 and 77 limit peptide of interest to glucagons-like peptide-1 derivative. The specification defines GLP-1 derivatives as following: "in addition to the above-mentioned GLP-1 (7-37) and

GLP-1(7-36) NH_2, there can be mentioned peptides having an insulinotropic activity in which amino acid residues have been substituted for, added to, and/or deleted from the peptide comprising 37 amino acid residues of GLP-1, peptides having an insulinotropic activity in which amino acids of said peptide have been further modified (for example, an amidated form), and peptides having an insulinotropic activity that are obtained from the combinations thereof" (paragraph bridging pages 11-12, emphasis added). Since the number of allowed substitutions, additions and/or depletions is not limited, the GLP-1 derivative can have the amino acid sequence with an unknown homology to human GLP-1.

Thus, the genus of DNAs that comprise the DNA molecules encoding GLP-1 and derivatives thereof is a large variable genus with the potentiality of encoding GLP-1 peptides from different natural sources such as hamster and human, for example, and many different man made derivative peptides. Therefore, many structurally and functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only four species of the claimed genus of fusion proteins comprising human GLP-1 (Figures 7 and 11-13). The specification does not disclose the isoelectric points of said fusion proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a GLP-1 derivative and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other peptide of interest. Therefore, the specification is insufficient to put

one of skill in the art in possession of the attributes and features of the species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 54-77, 79 and 94-96 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making derivatives of human GLP-1 using fusion proteins shown at Figures 7, 11-13 (SEQ ID NOs: 20-23) or said fusion proteins wherein a given GLP-1 derivative is substituted by any of GLP-1 derivatives recited in the specification (pages 12-13), does not reasonably provide enablement for a process of making a peptide of any structure and/or function or GLP-1 derivative using other helper and protective peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 54-77, 79 and 94-96 are directed to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a peptide of interest, a vector and a cell comprising said DNA.

Therefore, they are drawn to a method of making of a genus of a polypeptide of an unknown function and having any characteristics as long as the isoelectric point of the peptide of interest connected to a helper peptide is between 8 and 12. While the specification teaches a method of making of a

highly purified GLP-1 derivative , it does not provide any guidance as to a process for producing a highly purified peptide of any function and characteristics. This would involve designing a helper peptide-peptide of interest fusion with the only limitation of having isoelectric point in the wide range of 8-12. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find the helper peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use the fusion of protective peptide, helper peptide and peptide of interest in a claimed method.

The state of the art is such that it is unpredictable which helper should be used for each peptide of interest, to enable the claimed method for any peptide of interest, and the specification provides no guidance on the matter. With regard to claims 63-66, 69-71, 74, 75 and 77 and 94-96, the specification provides no guidance as to what are other helper peptides that can be used instead of the ones present in SEQ ID NOs: 20-23.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the

properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted *a priori*. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an appropriate purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 97 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 97 is confusing as referring to "the fusion protein as described by any one of claims 82 to 89" whereas claims 82-89 are drawn to a process.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 54-77, 79 and 94-96 are rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki et al.

Suzuki et al. (US Patent 5, 5,891,671) teach the production of the 7-37 fragment of glucagon-like peptide-1 (GLP-1) using an *E. coli* transformed with a DNA encoding a fusion protein comprising the protective peptide, helper peptide and 7-37 GLP-1 (columns 5 and 6, columns 17-20, Examples 11-14, claim 13). Said protective peptide is a fragment of *E. coli* β-galactosidase that is used in the instant invention and cleavage site is a Kex2 protease cleavage site as in the

instant invention. Absent evidence to the contrary the fusion of the helper peptide and the 7-37 GLP-1 fusion has the requisite pI.

The applied reference has a common inventor, Yuji Suzuki, with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Allowable Subject Matter

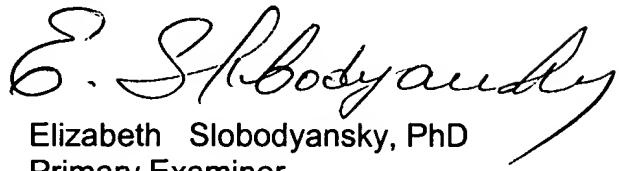
Claims 82 and 83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 97 would be allowable if rewritten to overcome the objection and the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

July 9, 2006